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First-line treatment for transplant-ineligible newly diagnosed multiple myeloma: a systematic review and Bayesian network meta-analysis of efficacy, safety, and high-risk subgroups

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - The authors declare no conflicts of interest. This study was conducted independently without pharmaceutical industry involvement.

INPLASY registration number: INPLASY202630023

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 March 2026 and was last updated on 7 March 2026.

INTRODUCTION

Review question / Objective In adults with transplant-ineligible newly diagnosed multiple myeloma (NDMM), what is the comparative efficacy and safety of six first-line treatment regimens — daratumumab plus lenalidomide and dexamethasone (DRd), daratumumab plus bortezomib, lenalidomide and dexamethasone (D-VRd), isatuximab plus bortezomib, lenalidomide and dexamethasone (Isa-VRd), carfilzomib plus lenalidomide and dexamethasone (KRd), bortezomib plus lenalidomide and dexamethasone (VRd), and lenalidomide plus dexamethasone (Rd) — as assessed by progression-free survival (PFS), overall survival (OS), and grade ≥3 adverse events, based on evidence from randomised controlled trials? Additionally, we aimed to evaluate comparative efficacy in patients with high-risk cytogenetics [del(17p), t(4;14), and/or t(14;16)].

Rationale Multiple myeloma is the second most common haematological malignancy, with the majority of patients aged 70 years or older and ineligible for autologous stem cell transplantation. Anti-CD38 monoclonal antibody-based regimens (DRd, D-VRd, Isa-VRd) have transformed first-line treatment, yet no head-to-head trials directly compare these regimens. Existing network meta-analyses (NMAs) are limited: Souto Filho et al. (Blood Cancer Journal, 2025) compared only four regimens without safety analysis or high-risk subgroup data; industry-sponsored NMAs carry

potential bias. A comprehensive, independent NMA incorporating all six guideline-recommended regimens, systematic safety comparison across multiple endpoints, and high-risk cytogenetics subgroup analysis is urgently needed to inform evidence-based clinical decision-making for this large patient population with significant unmet medical needs.

Condition being studied Multiple myeloma (MM) is a malignant neoplasm of terminally differentiated plasma cells. It accounts for approximately 10% of haematological malignancies, with an estimated 187,774 new cases and 121,252 deaths globally in 2022 (GLOBOCAN). The disease leads to end-organ damage including renal failure, bone disease, anaemia, and immunodeficiency. A substantial proportion of newly diagnosed patients are ineligible for autologous stem cell transplantation due to advanced age, comorbidities, or poor performance status. First-line treatment options for these transplant-ineligible patients have expanded significantly with the introduction of anti-CD38 monoclonal antibodies (daratumumab, isatuximab), proteasome inhibitors (bortezomib, carfilzomib), and immunomodulatory drugs (lenalidomide).

METHODS

Search strategy Electronic databases: PubMed/MEDLINE, Embase (via Ovid), and Cochrane Central Register of Controlled Trials (CENTRAL). Search date: from inception to 21 November 2025.

Search terms combined MeSH/Emtree terms and free-text keywords:
(1) Disease: "multiple myeloma" OR "plasma cell myeloma" OR "myelomatosis"
(2) Population: "newly diagnosed" OR "untreated" OR "transplant-ineligible" OR "transplant-non-eligible"
(3) Interventions: "daratumumab" OR "Darzalex" OR "lenalidomide" OR "Revlimid" OR "bortezomib" OR "Velcade" OR "carfilzomib" OR "Kyprolis" OR "isatuximab" OR "Sarclisa" OR "dexamethasone"
(4) Study design: "randomized controlled trial" OR "RCT" OR "clinical trial"

Supplementary sources: ClinicalTrials.gov, WHO ICTRP, conference abstracts from ASH, EHA, and ASCO (2018–2024), reference lists of included studies and relevant systematic reviews, and clinical trial databases of major pharmaceutical companies.

No language restrictions were applied.

Participant or population Adults (≥18 years) with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplantation (ASCT). Transplant ineligibility is defined as: age ≥65 years, presence of significant comorbidities, patient refusal of transplantation, or other clinical judgment deeming the patient unfit for transplant. Excluded: patients with relapsed or refractory multiple myeloma, transplant-eligible patients, and patients with other plasma cell neoplasms (e.g., Waldenström macroglobulinaemia, primary amyloidosis).

Intervention Six first-line treatment regimens:
(1) DRd: daratumumab + lenalidomide + dexamethasone
(2) D-VRd: daratumumab + bortezomib + lenalidomide + dexamethasone
(3) Isa-VRd: isatuximab + bortezomib + lenalidomide + dexamethasone
(4) KRd: carfilzomib + lenalidomide + dexamethasone
(5) VRd: bortezomib + lenalidomide + dexamethasone
(6) Rd: lenalidomide + dexamethasone

Sensitivity analysis additionally includes VMP (bortezomib + melphalan + prednisone) and D-VMP (daratumumab + VMP).

Comparator Within the network meta-analysis framework, all six regimens serve as mutual comparators. The reference comparators for the network are Rd and VRd, which form the two central nodes of the star-shaped evidence network.

Study designs to be included Randomised controlled trials (RCTs), primarily phase III clinical trials.

Eligibility criteria
Inclusion criteria:
- RCTs comparing two or more of the six target regimens in transplant-ineligible NDMM
- Reporting of PFS hazard ratio (HR) with 95% CI, or sufficient data to estimate HR
- English or Chinese language publications

Exclusion criteria:
- Non-randomised studies (observational studies, single-arm trials)
- Studies exclusively enrolling transplant-eligible or relapsed/refractory patients
- Duplicate publications (retaining the most complete or longest follow-up version)
- Studies with asymmetric treatment designs violating the transitivity assumption (e.g., COBRA

trial: KRd 24 cycles vs VRd 8 cycles then Rd maintenance)
- Conference abstracts with incomplete statistical data (e.g., missing confidence intervals).

Information sources Electronic databases: PubMed/MEDLINE, Embase (Ovid), Cochrane CENTRAL.
Trial registries: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP).
Conference proceedings: American Society of Hematology (ASH), European Hematology Association (EHA), American Society of Clinical Oncology (ASCO) annual meetings (2018–2024).
Other: reference lists of included studies and relevant systematic reviews; clinical trial databases of major pharmaceutical companies (Janssen, Sanofi, Amgen).

Main outcome(s) Primary outcome: Progression-free survival (PFS), defined as time from randomisation to disease progression or death from any cause. Effect measure: hazard ratio (HR) with 95% Bayesian credible interval (CrI). Treatment ranking: Surface Under the Cumulative Ranking curve (SUCRA).

Secondary efficacy outcome: Overall survival (OS), defined as time from randomisation to death from any cause. Effect measure: HR with 95% CrI.

Additional outcome(s) Safety outcomes: Incidence of grade ≥3 adverse events for seven endpoints:
(1) Neutropenia, (2) Infections, (3) Pneumonia, (4) Thrombocytopenia, (5) Anaemia, (6) Peripheral neuropathy, (7) Diarrhoea.
Effect measure: odds ratio (OR) with 95% confidence interval (CI).

Subgroup outcome: PFS in patients with high-risk cytogenetics [del(17p), t(4;14), and/or t(14;16)], measured as HR with 95% CI. Treatment ranking by P-score.

Data management Literature management: Zotero reference management software for deduplication and organisation. Data extraction: two independent reviewers extracted data using a pre-designed standardised form. Extracted information includes: study characteristics (trial name, NCT number, phase, design, sample size, median follow-up), patient baseline characteristics (age, sex, ECOG PS, ISS stage, cytogenetic risk), intervention details, and outcome data (HR with 95% CI for PFS and OS; event counts for adverse events). For studies not directly reporting HR, estimation methods included Tierney algorithm (from P-values or event counts) and Guyot algorithm (reconstruction of individual patient data from Kaplan-Meier curves). Disagreements resolved by discussion or third-party adjudication.

Quality assessment / Risk of bias analysis Risk of bias assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool across five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain rated as "low risk", "some concerns", or "high risk". Overall bias determined by the worst-performing domain. Two independent reviewers performed assessment; disagreements resolved by discussion or third-party adjudication. Publication bias assessed using comparison-adjusted funnel plots and Egger's regression test.

Strategy of data synthesis Bayesian network meta-analysis (NMA) using the gemtc package in R (version 4.3.0). For each outcome, both fixed-effect and random-effects models were fitted; model selection guided by deviance information criterion (DIC): DIC difference >5 favours the lower-DIC model; difference <3 favours the fixed-effect model (parsimony). Heterogeneity variance prior: informative log-normal prior (Turner et al.). Markov chain Monte Carlo (MCMC) sampling: 4 chains, 5000 burn-in, 50000 sampling iterations, thinning interval of 10. Convergence assessed by Brooks-Gelman-Rubin diagnostic (R-hat <1.05). Treatment ranking by SUCRA. Consistency assessed by node-splitting method.

Safety NMA: binary likelihood with logit link function; OR as effect measure. Due to incomplete adverse event reporting in SWOG S0777, safety analysis conducted in two subnetworks (DRd vs Rd; D-VRd/Isa-VRd/KRd vs VRd).

High-risk subgroup: frequentist NMA using the netmeta package; fixed-effect model; ranking by P-score.

Subgroup analysis Prespecified subgroup analysis: PFS in patients with high-risk cytogenetics, defined as presence of del(17p), t(4;14), and/or t(14;16) by fluorescence in situ hybridisation (FISH). ENDURANCE trial excluded from subgroup analysis as it systematically excluded high-risk patients by design (violating the transitivity assumption). Subgroup HR values extracted from published forest plots of individual trials. Fixed-effect frequentist NMA with P-score ranking. Results interpreted as exploratory given small subgroup sample sizes (17–48 patients per arm).

Sensitivity analysis Sensitivity analyses include:
(1) Extended network: inclusion of two additional trials (Real-MM: VMP vs Rd; ALCYONE: D-VMP vs VMP) to expand the network from 6 to 8 treatments and create a closed loop (Rd–VMP–VRd) enabling formal consistency testing.
(2) Comparison of SUCRA rankings between primary (6-treatment) and extended (8-treatment) networks to assess ranking stability.
(3) Fixed-effect versus random-effects model comparison for all outcomes.
(4) Assessment of the impact of individual trials on overall results through network geometry analysis.

Language restriction No language restrictions applied.

Country(ies) involved China.

Other relevant information This protocol was registered retrospectively after completion of the systematic review and network meta-analysis. The study was conducted in accordance with PRISMA 2020 guidelines and the PRISMA extension for network meta-analyses (PRISMA-NMA). The COBRA trial (NCT03729804, KRd vs VRd) was identified during screening but excluded due to: (1) mixed transplant-eligible/ineligible population with benefits driven by transplant-eligible patients; (2) asymmetric treatment design (KRd 24 cycles vs VRd 8 cycles then Rd); (3) interim conference abstract only with incomplete statistical data.

Included trials in primary NMA: IFM2017-3, CEPHEUS, SWOG S0777 (≥65 years subgroup), MAIA, ENDURANCE, IMROZ. Sensitivity analysis additionally includes Real-MM and ALCYONE.

This study is independent and received no pharmaceutical industry funding.

Keywords multiple myeloma; network meta-analysis; Bayesian; transplant-ineligible; first-line; anti-CD38; safety; high-risk cytogenetics.

Dissemination plans Results will be submitted for publication in a peer-reviewed international journal indexed in PubMed/MEDLINE. Key findings may be presented at major haematology conferences (ASH, EHA).

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